Why a National Committee?

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A bacterium cannot be clinically categorized as susceptible to an antibiotic in one hospital or country and resistant in another. The need for standardization of in vitro antibiotic susceptibility tests (the antibiogramme) appeared very soon, in the early 1950s. The World Health Organization convened in Geneva a first Expert Committee on Antibiotics in 1959 and a second in 1961 (WHO Technical Report Series 1959 No. 710 and 1961 No. 210). It immediately appeared that the Committee had to work in two fields: the methods and the interpretation of the data. However, it was also clear that the need for reference methods was a priority. In fact, the efforts devoted to define all the details of a reference method at WHO meetings and later were continuous until 1970. The problem of the clinical interpretation (determination of the breakpoints) seemed too controversial at the international level, and the second WHO Committee suggested that this area should be the concern of a 'National Authority'. Consequently, the role of a National Committee is mainly in the field of interpretation. Nevertheless, in the past 20 years an important number of new techniques, devices and machines (more or less automated) have been proposed to simplify and accelerate the work of clinical laboratories. All these approaches cannot be accepted without a control. A national network of medical microbiology laboratories specializing in antibiotic evaluation has to play a role in this control under the supervision of a National Reference Center for Antibiotics. Evaluation of a new technique is not always easy. Some methods provide values that can be directly compared with the MIC determined by the reference methods defined at the international level. However, many others, automated or not, are intended to directly characterize clinically the strains studied. In certain instances, it is possible, using the basic principle of the proposed new technique, to perform a quantitative study in an attempt to correlate its results with those of the reference method. When this is not possible, the study of reference strains from the National Reference Center may provide a good approximation to decide if the technique is valuable or not, or has to be adjusted. Many of these evaluations can be performed in agreement with the manufacturer, who provides supplementary information and materials. The results are often confidential or not sufficient to justify a scientific publication. Since the clinical laboratories of a country need to be informed of the exact value of a new technique, the role of the National Committee is important in discussion and in informing all the medical microbiology laboratories. Such a Committee is even worthwhile for the adequate use of the new methods nationwide.

As already pointed out, the major role of a National Committee is to decide on values of the breakpoints that delineate the clinical categories. The subject is controversial, as pointed out by Garrod at the first WHO meeting, because of the two definitions of resistance. The first is related to the pharmacologic data on the antibiotic concentrations achieved at the site of infection. The second is related to genetic alterations of the bacteria which, consequently, allow growth in the presence of an antibiotic concentration higher than that inhibiting the so-called susceptible bacteria. This latter notion has been exemplified since 1947 by the β-lactamase-producing strains of staphylococci. Depending on the relative importance attributed to one or the other factor, the value of the breakpoint relies heavily on judgment and experience. It is important to specify the various factors that have to be taken into account at a national level to adopt a particular breakpoint. All antibiotics are not widely used at the same time in all countries, in particular the recent molecules. The need for breakpoints is especially urgent when a new drug appears on the market. The breakpoints cannot be selected irrespective of those already chosen for the other members of the antibiotic family. A National Committee has to balance the intrinsic activity and the pharmacology of the new drug comparatively with the other members of the same family. Under certain circumstances, a particular

breakpoint has to be chosen in case of special dosage, route, site of infection, or groups of bacteria. These values vary from one country to another depending on the therapeutic habits and predominant infections. All these local problems have to be taken into account by a National Committee. A new resistance character can emerge and be widespread in one country, and it is important to provide information to the clinical laboratories in order to detect it. In the past 20 years, a considerable amount of work has been devoted to the study of antibiotic-inactivating enzymes, structural modifications of the targets, and their genetic basis. The 'analytical approach' or 'interpretive reading' of the resistance characters correlated with these modifications is intended to define them by means of their phenotypic behavior or by molecular studies (probes or polymerase chain reaction (PCR), for example). Some of these new characters lead to low-level or intermediate categories of resistance. Their clinical consequences may be questionable. Modification of breakpoints of an antibiotic family based on the existence of this type of resistance mechanisms needs collaborative in vitro, experimental or clinical studies that can be undertaken by a group under the authority of a National Committee.

To face all these problems, the *Comité de l'Antibiogramme de la Société Française de Microbiologie* was created in 1980. It included 20 members: bacteriologists specializing in antibiotics, pharmacologists and clinicians. Collaborative studies were performed in the laboratories of the group members and the results reported in an annual meeting where modifications or new breakpoints were discussed and accepted. A *communiqué* reviewing all the breakpoints is annually published in the abstract book of the Interdisciplinary Meeting on Anti-infectious Chemotherapy, which takes place every December in Paris, and also with the proceedings of the meeting that are published in a special issue of the journal *Pathologie et Biologie*.

Representatives of a National Committee must be natural members of regional (European) or international groups trying to establish common values for interpretation of in vitro susceptibility testing methods. An excellent example of the methodology to achieve a broad agreement is the International Collaborative Study working in the field of reference methods. From 1961 to 1968, a working group of 20 directors of laboratories from 11 countries engaged in susceptibility testing prepared 40 reports which were exchanged and discussed on numerous occasions in Stockholm, Geneva, and at international congresses. The final draft, written by Hans M. Ericsson and John C. Sherris, was sufficiently documented to be widely accepted. In the field of interpretation, the same type of organization exists only at the national level in certain countries. However, committees, governmental offices or manufacturers propose breakpoints without any explanation of the criteria for their choice. It seems difficult to establish common values without a collaborative organization able to remedy this lack of information. Justification of choices and documents must be exchanged before any discussion. Administrative regulations cannot be imposed without documented discussion by all the scientific people engaged in the field of antibiotics.